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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DEJONG, ERIC S	
ART UNIT	PAPER NUMBER
1631	
MAIL DATE	DELIVERY MODE
05/15/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/816,755	VAIDEHI ET AL.	
	Examiner	Art Unit	
	ERIC S. DEJONG	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,35,37-57 and 59-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,35,37-57 and 59-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/13/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Applicants response filed 02/13/2008 is acknowledged.

Claims 2, 4-34, 36, and 58 are cancelled. Claims 1, 3, 35, 37-57, and 59-64 are pending and currently under examination.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 02/13/2008 has been considered by the examiner and a signed copy has been included with this Office action.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 3, 35, 37-57, and 59-64 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. This rejection is newly applied.

Claims 1, 3, 35, 37-57, and 59-64 are drawn to a computer-implemented method for predicting a three-dimensional structure of a G-protein coupled receptor having a plurality of α-helical regions. The recited process involves the abstract/computational steps of identifying ranges of amino acids in a sequence of a G-protein coupled receptor as transmembrane regions, constructing two or more helices for the transmembrane regions, obtaining an optimized structure for each of the two or more helices, assembling the optimized structures of the two or more helices into a helix bundle configuration, optimizing the helix bundle configuration with a lipid bi-layer using a first molecular dynamics simulation, constructing one or more inter-helical loops to generate a full atom model, and optimizing the full-atom model using a second molecular dynamics simulation and, therefore, involves the application of a judicial exception. Regarding inventions involving the application of a judicial exception, said application must be a practical application of the judicial exception that includes either a step of a physical transformation, or produces a useful, concrete, and tangible result (State Street Bank & Trust Co. v. Signature Financial Group Inc. CAFC 47 USPQ2d 1596 (1998), AT&T Corp. v. Excel Communications Inc. (CAFC 50 USPQ2d 1447 (1999)). In the instant claims, there is no step of physical transformation that results from said application of judicial exception, thus the Examiner must determine if said application of a judicial exception produces a useful, concrete, and tangible result.

A tangible result requires that the claim must set forth a practical application of a judicial exception to produce a real-world result . Claims 1, 3, 35, 37-57, and 59-64 are not limited to producing only tangible results. It is acknowledged that the instant claims

have recite a generic step for "outputting a predicted structure for the G-protein coupled receptor" (see line 16 of claim 1). However, upon review, the instant specification teaches that "outputting", as recited in the instant claims, encompasses embodiments wherein outputting results only in the transmission of data and information (see page 22, lines 2-8), which reads on the transient, non-statutory embodiments of generating a signal or carrier wave. See *In re Nuitjen* (2007).

For the benefit of applicants, an amendment to the instant claims so as to recite "outputting **to a user** a predicted structure for the G-protein coupled receptor" (emphasis added) would be sufficient to overcome the instant rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 35, 37-39, 41-46, 48, and 51-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Biggin et al., *Biophysical Chemistry* (1999) (see references cited by Examiner, mailed 01/14/2005) in view of van Rhee et al., *Drug Development Research* 37:1-38 (1996). This rejection is maintained and reiterated from the previous Office action.

Biggin et al. discloses novel method and related computer systems for simulating and predicting the structure of membrane bound proteins comprising a plurality of α-helices (See Biggin et al., Abstract et al.). Biggin et al. further teaches the computational molecular modeling of bacteriorhodopsin protein comprising set 7 helices comprising transmembrane regions (page 169, Table 1). Biggin et al. discloses using mean-field membrane simulations (first simulation) to obtain information about possible conformations and/or orientations of a protein (pages 166-170, §§6.1 to 6.2). Biggin et al. discloses an all atom simulation (page 170, §7) applied to TM helix bundle models may be constructed by less costly simulations without bilayer, then refined (optimized) by subsequent (second simulation etc.) MD simulations in an atomistic bilayer or bilayer-mimetic environment. The membrane-mimetic environment has been used in two MD simulations of bundles of α-helices (citation) that have evolved into a coiled-coil (loop) tetrametric structure with a left handed twist (page 172, column 1, lines 3-28). Fluctuations in the structure over the course of the simulation were greater for inter-helix loops than for the TM helices (page 179, column 2, last 9 lines). The predicted

structures are output based on the all atom simulations (page 178, Figure 9). Biggin et al. discloses simulations of helix/bilayer interactions usually employ a hydrophobicity index to represent the presence of a lipid bilayer (page 166, column 2, §6.1, Second paragraph).

Biggin et al. discloses that inserting helices prefer to swing one end into the hydrophobic region, after first adopting a surface-bound orientation (page 167, column 2, last 5 lines), as in instant claims 38 and 44. Fluctuations in the structure over the course of the simulation were greater for inter-helix loops than for the TM helices (page 179, column 2, last 9 lines). Simulations of N=5, 6, 7, and 8 bundles yielded stable (rigid body) helical bundles (page 179, column 1, second paragraph). The simulation studies of Biggin et al. are directed to various solvent environments (page 171, column 1, lines 1-2). The simulation method of Biggin et al. comprises the approximation of a lipid bilayer as directed to free energy in a solution wherein the Poisson-Boltzman equation has been used to provide a continuum expression for the electrostatic potential due to the lipid headgroups and water (page 167, column 2). Biggin et al. further discloses that simulations are performed over a 100 ps time frame (page 175, column 1, lines 6-8).

While Biggin et al. sets for the above described structural prediction and computational modeling of transmembrane α-helical proteins, for example, bacteriorhodopsin, Biggin et al. does not expressly teach predicting the structure of a G-protein coupled receptor as instantly claimed.

van Rhee et al. discloses the analysis and review of G protein-coupled receptors of the rhodopsin-related family members to draw inferences from amino acid sequences

for single receptors and multiple sequence alignments with regard to the molecular architecture of this class of receptors (see van Rhee et al., Abstract and page 6, col. 1, line 45 through page 8, col. 1, line 24).

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to use the structural prediction and computational modeling methods of transmembrane α-helical proteins, such as bacteriorhodopsin, as taught by Biggin et al. for predicting the structure of a G protein-coupled receptor because van Rhee et al. teaches that the use and analysis rhodopsin-related proteins for modeling the architecture (structure) of G protein-coupled receptors. One of skill in the art would have a reasonable expectation of success because Biggin et al. explicitly discloses the modeling of the transmembrane α-helical proteins bacteriorhodopsin and van Rhee et al. is directed to the modeling of G protein-coupled receptors in the rhodopsin-related family.

Claims 1, 3, 35, 37-39, 40-46, and 49-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Biggin et al., *Biophysical Chemistry* (1999) (see references cited by Examiner, mailed 01/14/2005) in view of van Rhee et al., *Drug Development Research* 37:1-38 (1996), as applied to claims 1, 3, 35, 37-39, 41-46, 48, and 51-64 above, and further in view of Mathiowetz et al., *Proteins* (1994) (see the IDS filed 02/15/2002). This rejection is maintained and reiterated from the previous Office action.

As discussed above, Biggin et al. in view of van Rhee et al. sets forth methods and related computer systems for simulating and predicting the structure of rhodopsin-

related G protein-coupled receptors and membrane bound proteins comprising a plurality of α-helices. However, neither Biggin et al. nor van Rhee et al. expressly teach the use of Newton-Euler Inverse Mass Operator in molecular dynamics simulations or the treatment of counterions as set forth in claims 40, 49 and 50.

Mathiowetz et al. discloses improved methods for molecular dynamics simulation of proteins comprising the cell multiple method for nonbond interactions and the Newton-Euler Inverse Mass Operator (see Mathiowetz et al., Abstract and throughout), which reads on the Newton-Euler Inverse Mass Operator in molecular dynamics simulations and treatment of counterions as recited in claims 40, 49 and 50.

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to employ the cell multiple method for nonbond interactions and the Newton-Euler Inverse Mass Operator, as taught by Mathiowetz et al., in combination with the structural prediction and computational modeling methods of transmembrane α-helical proteins, such as bacteriorhodopsin, as taught by Biggin et al., for predicting the structure of a G protein-coupled receptor because Mathiowetz et al. teaches that the new methods provide improvements for molecular dynamics modeling. One of skill in the art would have a reasonable expectation of success because the methods taught by Mathiowetz et al. are directed to improvements on known computational modeling methods for protein modeling and structure determination.

Claims 1, 3, 35, 37-39, 41-48, and 51-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Biggin et al., *Biophysical Chemistry* (1999) (see references cited by Examiner, mailed 01/14/2005) in view of van Rhee et al., *Drug Development Research* 37:1-38 (1996), as applied to claims 1, 3, 35, 37-39, 41-46, 48, and 51-64 above, and further in view of Mayo et al., *J. Phys. Chem.* (1990) (see the IDS filed 02/15/2002). This rejection is maintained and reiterated from the previous Office action.

As discussed above, Biggin et al. in view of van Rhee et al. sets forth methods and related computer systems for simulating and predicting the structure of rhodopsin-related G protein-coupled receptors and membrane bound proteins comprising a plurality of α-helices. However, neither Biggin et al. nor van Rhee et al. expressly teach the use of a DREIDING force field.

Mayo et al. describes a method requiring new parameters, DREIDING, useful for predicting structures and dynamics of organic, biological, and main-group inorganic molecules (Abstract and throughout), which reads on the use of a FREIDING force field in molecular dynamics simulations as recited in claim 47.

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to employ a DREIDING force field, as taught by Mayo et al., in combination with the structural prediction and computational modeling methods of transmembrane α-helical proteins, such as bacteriorhodopsin, as taught by Biggin et al., for predicting the structure of a G protein-coupled receptor because Mayo et al. teaches the DREIDING force field as an improvement over as it provides a generic force field that is useful in predicting

structures of organic, biological, and main-group inorganic molecules. One of skill in the art would have a reasonable expectation of success because the computational modeling of a membrane proteins involves the consideration of both hydrophobic and hydrophilic (organic/inorganic) molecular environments.

Response to Arguments

Applicant's arguments filed 02/13/2008 have been fully considered but they are not persuasive.

In regard to applicants request for consideration of the provisions of MPEP § 707.02, applicants point out that applications up for a third action and have been pending for more than 5 years should be carefully reviewed by the supervisory patent examiner.

In response, it is noted that supervisory patent examiner, Marjorie Moran, was present and participated in the interview conducted on 10/09/2007, as noted in the Examiner interview summary mailed 10/15/2007 and the interview summary provided by applicants in the current response (see the first page of applicants remarks, filed 02/13/2008).

In regard to applicants request for consideration of the provisions of MPEP § 716.04, applicants request that the Office specifically point out previous grounds of rejection are now considered a “clear error”.

In response, it is noted that the claims set filed 06/25/2007 contained significant amendments that altered the scope and subject matter of the instant claims. Upon review, the previous Office action set fort that the amendments made to the claims set filed 06/25/2007 were sufficient to over come the previous grounds of rejection (see pages 2 and 3 of the Office action, mailed 09/14/2007). It is further noted that the amendments made to the claims set filed 06/25/2007 necessitated the new ground of rejection under 35 USC 103(a) (see pages 4-10 of the Office action mailed 09/14/2007). Further, it is not agreed that the amendments made to the claims set filed 06/25/2007 contained only the newly recited term "G-protein coupled receptors" as argued by applicants. See for example claim 1, lines 2, 4-6, 11, 12, 1419, and 20 of the claim set filed 06/25/2007.

In regard to the rejection of claims 1, 3, 35, 37-39, 41-46, 48, and 51-64 are under 35 U.S.C. 103(a) as being unpatentable over Biggin et al., in view of van Rhee et al., applicants argue at a minimum in order to establish obviousness of a claim, the prior art reference or references when combined, must teach or suggest every claim limitation of the claimed invention. Applicants further argue that the rational for obviousness must establish why one of skill in the art would have modified the references to arrive at the elements recites in applicants claims.

In response, applicants argument directed to the application of a strict TSM test are not persuasive. It is first noted that the recent Supreme Court decision in KSR Intl. Co. v. Teleflex Inc. rejected the rigid approach of applying a strict TSM test as the sole

basis for obviousness and *that the analysis for obviousness need not seek out precise teachings directed to the specific subject matter of a claim (emphasis added)*. Further the decision set forth that the analysis can take into account the inferences and creative steps that a person of ordinary skill in the art could employ and that a person of ordinary skill in the art is also a person of ordinary creativity, not an automaton. Further, the decision set forth that a combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.

Applicants further presents arguments directed to why Biggin et al. does not anticipate the instant claims and cites as support applicants amendment and responses filed 01/19/2006 and 09/27/2006.

In response, it is noted that the instant claims are not rejected under 35 USC §102 as being anticipated by Biggin et al. Rather, the instant claims are rejected under 35 USC 103(a) as being unpatentable over Biggin et al., in view of van Rhee et al. Therefore applicants argument is not persuasive. Further, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants further argue that Biggin et al. does not disclose the step of "after optimizing the helix bundle configuration, constructing one or more inter-helical loops to

generate a full-atom model of the G-protein coupled receptor", "obtaining an optimized structure for each of the two or more helices", assembling the optimized structure for the two or more helices into a helical bundle configuration" and, further, that Biggin et al. does not describe a method that involves dissecting protein structure at various levels of complexity. Applicants further argue that van Rhee does not account for these omissions.

In response, the limitations indicated by applicants are expressly taught by Biggin et al. Biggin et al. on page 162, col. 2, lines 25-31, teaches a two stage modeling approach wherein stable units of a trans-membrane helix is form and then assembled into a tertiary structure (i.e. a bundle of transmembrane helices). Further, Biggin et al. expressly describes the analysis of complex transmembrane protein structures that interact with a lipid bilayer (see Biggin et al., Title and Abstract). Contrary to applicants argument, the disclosed modeling approach is directed to modeling only those protein domains that interact with a lipid bilayer and, therefore, involves dissecting protein structure at various levels of complexity as instantly claimed.

Applicants further argue that the invention provides a computational hierarchical strategy for predicting the structure of certain transmembrane proteins such as G-protein coupled receptors and, by contrast, Biggin et al. only describes single simulations on membranes. Applicants further argue that van Rhee does not account for these omissions.

In response, it is further noted that Biggin et al. does expressly teach an example involving a two stage modeling approach wherein separate modeling computations are performed to arrive at a transmembrane helical bundle (Biggin et al. on page 162, col. 2, lines 25-31). Therefore applicants argument is not persuasive.

Applicants further argue that it is clear Biggin et al. acknowledges that accurate prediction of a membrane protein structure was not possible at the time of writing.

In response, it is not agreed that Biggin et al. provides any explicit teaching that accurate prediction of a membrane protein structure was not possible at the time of writing. Contrary to applicants argument, the citation of Biggin et al. (see page 175, col. 1, line 9 through col. 2, line 2) relied upon by applicants demonstrates that MD simulations of trans-membrane helices are feasible and that such computational modeling allows for the prediction of membrane protein structures.

Applicants further argue that the claimed method can predict a protein structure without prior knowledge of it, whereas Biggin et al. references only simulation of a system whose structure is known as a gauge of the accuracy of a single simulation.

In response, it is noted that the instant claims do not recite any limitation wherein the three-dimensional structure of a G-protein coupled receptor used in the recited modeling procedure is required to be a protein of unknown structure. Therefore applicants argument is not persuasive.

Applicants further argue that the combination of Biggin et al. and van Rhee et al. does not render the instant claims obvious because to derive applicants invention from such a combination it would be necessary to insert steps not explicitly taught by Biggin et al. or other cited references.

In response, the deficiencies of Biggin et al. argued by applicants are not found persuasive for the reasons provided above. Therefore applicants argument is not persuasive.

It is further noted that applicants have not provided any specific arguments directed to the separate rejection of claims under 35 U.S.C. 103(a) as being unpatentable over Biggin et al., in view of van Rhee et al., and further in view of Mathiowetz et al. as well the separate rejection of claims under 35 U.S.C. 103(a) as being unpatentable over Biggin et al., in view of van Rhee et al., and in further view of Mayo et al.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERIC S. DEJONG whose telephone number is (571)272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Moran Marjorie can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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